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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/070,728	03/11/2002	Joseph Sperling	02/23192	9736

7590 03/30/2004  
G E Ehrlich  
Anthony Castorina  
Suite 207  
2001 Jefferson Davis Highway  
Arlington, VA 22202

EXAMINER

RILEY, JEZIA

ART UNIT	PAPER NUMBER
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1637

DATE MAILED: 03/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

5/18

**Office Action Summary**

Application No.

10/070,728

Applicant(s)

SPERLING ET AL.

Examiner

Jezia Riley

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— The MAILING DATE of this communication appears on the cover sheet with the correspondence address —

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-23 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) \_\_\_\_ is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☒ None of:
- 1 ☒ Certified copies of the priority documents have been received.
- 2 ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
- 3 ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_



**DETAILED ACTION**

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-10, 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Hanna (US6,008,334).

Hanna discloses protected thiol analogs of pyrimidine bases for syntheses of DNA and RNA by chemical or enzymatic methods. The subject analogs include reagents suitable for DNA or RNA synthesis via phosphoramidite, H-phosphonate or phosphotriester chemistry as well as reagents suitable for use by RNA and DNA polymerase, including thermostable polymerases employed by PCR or other nucleic acid amplification techniques. The nucleotide analogs synthesized by methods of this invention can thus be incorporated into oligonucleotides or polynucleotides, deprotected

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and derivatized with a functional group. In some cases the protecting groups are themselves antigenic and may be left on the oligonucleotides or polynucleotides for detection with antibodies. A method of synthesizing oligonucleotides with a functional group using the subject nucleotide analogs is also provided (abstract). Hanna relates to pyrimidine nucleotide analogs which contain modified bases with protected thiol groups attached at a position on the base, preferably the 5 position, which is not involved in Watson-Crick base pairing. These nucleotide analogs are intermediates in chemical or enzymatic synthesis of DNA or RNA oligonucleotides and are therefore stable under conditions required for synthesis of these molecules. After synthesis, the protecting group on the analog is removable to generate a reactive thiol group. Once generated, the thiol group can be treated with thiol modifying reagents to attach functional groups such as crosslinking agents or reporter molecules. The thiol groups in these analogs are attached to the ring by either a three, four, or five carbon chain.

The method provides novel base-protected nucleotide analogs, both ribonucleotides and deoxynucleotides, that contain masked thiol groups on the 5 position of pyrimidines, which is not involved in Watson-Crick base pairing. These analogs can be incorporated into oligonucleotides via automated synthesis and isolated with the thiol protecting group intact. After removal of the thiol protecting group many types of functional groups, such as photocrosslinking agents, fluorescent tags, radioisotopes, biotin, reporter molecules, spin labels (e.g., commercially available proxyl or tempo), chemiluminescent, antigenic or other functional groups, can be site-specifically attached by utilizing thiol-modifying reagents. This feature adds a level of specificity to the



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oligonucleotide modifications not present with the amino-tagged analogs previously described, and enables examination of molecular interactions that are not directly at the nucleotide base by allowing functional groups to be placed at varying distances from the base or helix strand. Since these analogs have the functional group attached via the sulfur atom, some have the further advantage of being cleavable under conditions which will not degrade or modify the oligonucleotide.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanna (US6,008,334) in view of Leone et al. (US6369206).

Hanna discloses protected thiol analogs of pyrimidine bases for syntheses of DNA and RNA by chemical or enzymatic methods. The subject analogs include reagents suitable for DNA or RNA synthesis via phosphoramidite, H-phosphonate or phosphotriester chemistry as well as reagents suitable for use by RNA and DNA polymerase, including thermostable polymerases employed by PCR or other nucleic acid amplification techniques. The nucleotide analogs synthesized by methods of this invention can thus be incorporated into oligonucleotides or polynucleotides, deprotected and derivatized with a functional group. In some cases the protecting groups are themselves antigenic and may be left on the oligonucleotides or polynucleotides for detection with antibodies. A method of synthesizing oligonucleotides with a functional group using the subject nucleotide analogs is also provided (abstract). Hanna relates to pyrimidine nucleotide analogs which contain modified bases with protected thiol groups attached at a position on the base, preferably the 5 position, which is not involved in Watson-Crick base pairing. These nucleotide analogs are intermediates in chemical or enzymatic synthesis of DNA or RNA oligonucleotides and are therefore stable under conditions required for synthesis of these molecules. After synthesis, the protecting group on the analog is removable to generate a reactive thiol group. Once generated, the thiol group can be treated with thiol modifying reagents to attach functional groups such as crosslinking agents or reporter molecules. The thiol groups in these analogs are attached to the ring by either a three, four, or five carbon chain.



The method provides novel base-protected nucleotide analogs, both ribonucleotides and deoxynucleotides, that contain masked thiol groups on the 5 position of pyrimidines, which is not involved in Watson-Crick base pairing. These analogs can be incorporated into oligonucleotides via automated synthesis and isolated with the thiol protecting group intact. After removal of the thiol protecting group many types of functional groups, such as photocrosslinking agents, fluorescent tags, radioisotopes, biotin, reporter molecules, spin labels (e.g., commercially available proxyl or tempo), chemiluminescent, antigenic or other functional groups, can be site-specifically attached by utilizing thiol-modifying reagents. This feature adds a level of specificity to the oligonucleotide modifications, and enables examination of molecular interactions that are not directly at the nucleotide base by allowing functional groups to be placed at varying distances from the base or helix strand. Since these analogs have the functional group attached via the sulfur atom, some have the further advantage of being cleavable under conditions which will not degrade or modify the oligonucleotide.

Leone et al. discloses metal cluster compounds, and a process for making such compounds. The compounds may be generally described as organothiol metal clusters, wherein the metal core is comprised of gold, platinum, silver, palladium or combinations of these metals. Prominent among the disclosed organometallic compounds is a large palladium and platinum cluster compound. The metal core of the compounds, wherein Gold is the prominent metal, is about 1.4 nm in diameter and comprises about 50 to about 70 metal atoms. There are about 12 metal atoms on the surface of each cluster, and each surface metal atom is bound to an organic group by a thiol (M-S) bond.

Therefore it would have been obvious at the time the invention was made to attached metal cluster as taught by Leone et al. to the analogs of Hanna. The motivation is that such many types of functional groups, such as photocrosslinking agents, fluorescent tags, radioisotopes, biotin, reporter molecules, spin labels (e.g., commercially available proxyl or tempo), chemiluminescent, antigenic or other functional groups, can be site-specifically attached by utilizing thiol-modifying reagents. This feature adds a level of specificity to the oligonucleotide modifications, and enables examination of molecular interactions that are not directly at the nucleotide base by allowing functional groups to be placed at varying distances from the base or helix strand. (Hanna Col. 3). And the probes of Leone have demonstrated sensitivities significantly greater than many currently used technologies, including radioactive labeling, fluorescent labeling and colloidal gold. The increased sensitivity of the probes, most notably, those probes of the embodiment wherein the metal in the cluster is palladium or platinum, will, in turn, allow for earlier detection of harmful infections or conditions, with fewer antigen test strips needed, fewer false-positive results, and smaller biopsied specimens. Furthermore, the present invention avoids the use of radioactive or highly toxic materials, which are very costly and difficult to dispose of and impose limitations on many currently used technologies (Leone col. 5-6).

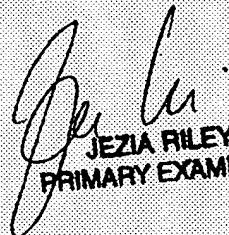


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jezia Riley whose telephone number is 571-272-0786. The examiner can normally be reached on 9:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

March 27, 2004

  
JEZIA RILEY  
PRIMARY EXAMINER